Autophagy and neurodegeneration: Pathogenic mechanisms and therapeutic opportunities

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In Brief

This review discusses the importance of autophagy function for brain health, outlining connections between autophagy dysfunction and neurodegenerative disorders. The potential for autophagy as a therapeutic strategy for neurodegenerative disease is discussed, along with how this may be achieved.

Summary

Autophagy is a conserved pathway that delivers cytoplasmic contents to the lysosome for degradation. Here we consider its roles in neuronal health and disease. We review evidence from mouse knock-out studies demonstrating the normal functions of autophagy as a protective factor against neurodegeneration associated with intracytoplasmic aggregate-prone protein accumulation, as well as other roles including in neuronal stem cell differentiation. We then describe how autophagy may be affected in a range of neurodegenerative diseases. Finally, we describe how autophagy upregulation may be a therapeutic strategy in a wide range of neurodegenerative conditions and consider possible pathways and druggable targets that may be suitable for this objective.

Autophagy cell biology

Macroautophagy (henceforth autophagy) is a major intracytoplasmic protein degradation pathway whereby cytoplasmic contents are delivered, by double-membraned vesicles called autophagosomes, to the lysosome for degradation. It should be differentiated from other pathways that will not be considered in this review, like chaperone-mediated autophagy and microautophagy, where substrates are directly translocated into the lysosome without vesicular transport. The first morphologically characteristic structure in autophagy is the double-membraned cup-shaped autophagosome precursor called the phagophore that engulfs substrates as its edges extend. After the phagophore edges close to form a vesicle,

the completed autophagosomes traffic along microtubules to enable autophagosome-lysosome fusion, which leads to the degradation of the autophagic contents (figure 1). Autophagy is regulated by a series of proteins defined as ATG (AuTophaGy-related) proteins.

Autophagy was initially characterized as a bulk and non-selective degradation pathway induced by nutrient deprivation. However, more recent studies made clear that autophagy also contributes to intracellular homeostasis in non-starved cells by degrading cargo material, such as aggregate-prone proteins, including those causing many neurodegenerative conditions (aggrephagy), damaged mitochondria (mitophagy), excess peroxisomes (pexophagy) and invading pathogens (xenophagy) (Stolz et al., 2014). In the classic example, aggregates of aberrantly folded proteins are tagged with ubiquitin chains, which are recognized by ubiquitin-binding domain-containing receptors, such as p62/SQSTM1 (Sequestosome 1) (Bjørkøy et al., 2005), NBR1 (Neighbor Of BRCA1 Gene 1) (Kirkin et al., 2009), OPTN (optineurin) (Wild et al., 2011), TAX1BP1 (Tax1 binding protein 1), NDP52/CALCOCO2 (Nuclear Dot Protein 52 (Newman et al, 2012), TOLLIP (TOLL interacting protein) (Lu et al., 2014) and 26S proteasome regulatory subunit (RPN10) (Marshall et al., 2015) (Khaminets et al., 2016; Stolz et al., 2014). These receptors also contain LIR (LC3-interacting region) motifs in their sequences that can recognize the key autophagosome-associated protein, microtubule-associated protein 1 light chain 3 (LC3). Thus, these receptors serve as a bridge between ubiquitinated cargo and autophagosomes, and enhance the incorporation of cargo into autophagosomes for subsequent lysosomal degradation (Bjorkoy et al., 2005; Pankiv et al., 2007).

This concept of selective autophagy has now been extended with the description of precision autophagy. This is defined by the involvement of receptors with the ability to recognize LC3 family member proteins, their specific substrates and also, importantly, the capacity to act as platforms for the assembly of other core ATG factors (Kimura et al., 2015). To date, receptors identified in this class come from the TRIM family, a diverse group of proteins associated with the degradation of targets such as innate immunity signaling molecules (reviewed in Kimura et al., 2016). It seems likely that there are many other molecules that play such roles in autophagy and identifying them will be key for our understanding of autophagy in non-starved cells.

Key autophagy regulators

Autophagy activation in response to the primordial stimuli of nutrient deprivation and/or low cellular energy levels is mediated by signalling pathways that converge on ULK1/2 (mammalian homologs of the *C. elegans* uncoordinated-51 kinase) (figure 2). ULK1/2 forms a complex with ATG13, ATG101 and FIP200 (focal adhesion kinase family interacting protein of 200 kD). Nutrients and growth factor availability and levels of AMP/ATP (which reflect the energetic status of the cell) are sensed by mammalian target of rapamycin complex 1 (mTORC1) and AMP-dependent protein kinase (AMPK), respectively, which, in turn, oppositely regulate the ULK1/2 complex through a series of phosphorylation events. For instance, activation of AMPK by allosteric binding of AMP and phosphorylation of Thr172 promotes autophagy by directly activating ULK1 through phosphorylation of Ser 317 and Ser77 under glucose deprivation (Kim et al., 2011), or Ser 555 under amino acid starvation and mitophagy (Egan et al., 2011). On the other hand, in media replete with amino acids (sensed by the Rag-Ragulator complex) and growth factors (that signal by receptor tyrosine kinases and the PI3K/AKT pathway), mTORC1 is activated and inhibits autophagy by binding to the ULK1 complex (via Raptor-ULK1 interaction), and by phosphorylating both ATG13 and ULK1 (at Ser 757), thereby suppressing ULK1 kinase activity and preventing the interaction between ULK1 and AMPK (Ganley et al., 2009; Hosokawa et al., 2009; Jung et al., 2009; Laplante and Sabatini, 2012).

Activation of the ULK complex is required for the recruitment of the class III PI 3-kinase, VPS34, to the phagophore initiation sites where VPS34 generates phosphatidylinositol 3-phosphate (PI3P), while in a complex with VPS15, ATG14 and Beclin 1.The exact functions of PI3P in autophagy are still unclear. However, it appears to aid the recruitment of WD repeat domain phosphoinositide-interacting (WIPI) proteins to the phagophore membrane, which, in turn, control the recruitment of crucial downstream autophagic proteins (e.g., ATG16L1 by WIPI2) that dictate where the phagophores form (Dooley et al., 2014).

The ATG12 and ATG8/LC3 ubiquitin-like conjugation systems are then required for sustaining the expansion of the phagophore. In the first system, ATG12 is conjugated to ATG5, in a reaction that involves ATG7 and ATG10 (E1-like and E2-like enzymes, respectively), and the resulting complex binds non-covalently to ATG16L1. ATG12-ATG5-ATG16L1 associates with pre-autophagosomal membranes enabling their elongation by assisting in the recruitment of LC3. However, before this can happen, LC3 has to be processed by the cysteine protease ATG4 that cleaves the C-terminus of LC3 exposing a glycine residue (LC3-I form). This cleavage is crucial for LC3-I conjugation to phosphatidylethanolamine (PE), by a mechanism dependent on ATG7, ATG3 and ATG12-ATG5-ATG16L1 (E1-like, E2-like and E3-like enzymes, respectively), leading to the

formation of LC3-II, which is tightly associated with autophagosomal membranes. This cascade of reactions then sustains extension of the phagophore edges and its closure, to form mature autophagosomes (Bento et al., 2016b).

Extension of the phagophore is also assisted by mATG9, the only identified multi-pass transmembrane protein among the core ATG proteins. This protein appears to localize to the *trans*-Golgi network and the endocytic compartment, including early endosomes, late endosomes and recycling endosomes, and is postulated to aid in the supply of lipid-bilayers to the nascent phagophore, enabling its further elongation, prior to closure of the fully formed autophagosome (Bento et al., 2016b). This late stage, where the outer and the inner membranes of the pre-autophagosomal structure become separate entities, is poorly understood, but ATG2 in combination with WIPI1 appear to regulate autophagosome closure (Velikkakath et al., 2012), a process likely involving membrane fission/scission type events akin to the genesis of multi-vesicular bodies by ESCRT (endosomal sorting complexes required for transport)-mediated membrane budding (Knorr et al., 2015).

The source of autophagosome membranes is an area of active investigation. Endoplasmic reticulum (ER), Golgi and trans-*Golgi* network, mitochondria, plasma membrane and endosomal compartments have all been suggested as possible sources of phagophore-membranes (Bento et al., 2016b). The ER emerged as one of the possible sources of membrane for pre-autophagosomes not only because isolation membranes were observed cradled within a subdomain of the ER and interconnected with it (Axe et al., 2008; Hayashi-Nishino et al., 2009), but also because ATG14- and ATG5-positive isolation membranes were found in close proximity to a subdomain of the ER in contact with mitochondria during starvation (Hamasaki et al., 2013). Post-Golgi tubulo-vesicular compartments undergoing remodelling and homotypic fusion (Guo et al., 2012; Orsi et al., 2012; Young et al., 2006), and the ER-Golgi intermediate compartment (ERGIC) have also been considered as pre-autophagosomal membrane sources (Ge et al., 2013; Ge et al., 2014). The ERGIC was specifically observed to bud LC3-lipidation active vesicles that may enable autophagosome biogenesis and expansion (Ge et al., 2013; Ge et al., 2014).

The plasma membrane and the endocytic compartments are also suggested as membrane sources for early autophagosomal-precursor structures. Clathrin-dependent endocytosis has been implicated in this process by delivering ATG16L1 and mATG9 to recycling endosomes (via different routes and involving VAMP3-dependent membrane fusion events), which leads to the formation of early autophagosomal structures and mature autophagosomes (Moreau et al., 2011; Puri et al., 2013; Ravikumar et al., 2010). Over-expression of the recycling

endosome proteins TBC1D14 (a Rab11-effector) or PX-containing SNX18 were shown to induce accumulation of mATG9 and ATG16L1, respectively, along with other autophagic proteins (e.g., ULK1 and LC3) in this compartment (Knaevelsrud et al., 2013; Lamb et al., 2016; Longatti et al., 2012), reinforcing the possible role of recycling endosome as an important phagophore-membrane source.

Transcriptional regulation of autophagy

In addition to phosphorylation, discussed above, autophagy is also regulated at the transcriptional level. mTORC1, apart from regulating the ULK1/2 complex, also connects the lysosome nutrient-sensing (LYNUS) machinery to the transcriptional regulation of autophagy genes via transcription factor EB (TFEB) (Settembre et al., 2012). In resting cells, phosphorylation of TFEB by active mTORC1 induces TFEB binding to 14-3-3 proteins and therefore TFEB retention in the cytosol (Roczniak-Ferguson et al., 2012; Settembre et al., 2011). However, under starvation and consequent mTORC1 inactivation, TFEB is no longer phosphorylated and translocates to the nucleus, where it binds to CLEAR (Coordinated Lysosomal Expression and Regulation) consensus sequences in promoters of target genes and induces their transcription. Among these genes, many are directly related to the lysosome and autophagy (e.g. lysosomal hydrolases, vATPase subunits, ATG proteins) and thus TFEB appears to co-ordinately regulate the expression of many of the key genes required for autophagy/lysosome function (Sardiello et al., 2009; Settembre et al., 2011). ZKSCAN3 (zinc-finger protein with KRAB and SCAN domains 3) is a transcriptional repressor of autophagy that appears to oppose TFEB. ZKSCAN3 silencing enhances autophagosome and lysosomal biogenesis, and mTORC1 inhibition induces its accumulation in the cytosol (Chauhan et al., 2013). More than 20 other transcription factors have now been linked to transcriptional regulation of autophagy following a wide range of stimuli (Fullgrabe et al., 2014). For instance, microphthalmia-associated transcription factor (MITF) (which belongs to the same family of proteins as TFEB) (Martina et al., 2014), p53 (Kenzelmann Broz and Attardi, 2013) and forkhead box O3 (FOXO3) (Mammucari et al., 2007) have all been shown to trans-activate ATG genes.

Autophagy physiology and the nervous system

The mammalian nervous system requires autophagy to maintain its normal functions and homeostasis. Since ubiquitous deletion of core autophagy genes results in neonatal and embryonic lethality, multiple nervous system-specific knock-out mouse models have been generated to allow analyses of the roles of autophagy in neuronal function. A Nestin-Cre

promoter, that switches on embryonically in neuronal precursor cells has been used to excise floxed alleles of *Atg5* and *Atg7*. This results in autophagy deficiency in neuronal cells and glia accompanied by the accumulation of intra-neuronal aggregates (Hara et al., 2006; Komatsu et al., 2006; Komatsu et al., 2007a). The accumulation of these aggregates in otherwise normal mice suggests that autophagy plays a key role in removing aggregate-prone proteins, supporting earlier studies in cell culture models of Huntington's disease (Ravikumar et al., 2002). Subsequent Nestin-Cre models have been generated targeting *FIP200* and *Wipi4* as well as a double-knockout for *Ulk1/2* (Joo et al., 2016; Liang et al., 2010; Orosco et al., 2014). The result in all models is reduced survival, and early onset, progressive neurodegeneration across broad areas of the brain. However, the nature of pathology varies according to the gene targeted e.g. progressive spongiosis is seen in *FIP200* Nestin-Cre mice but not the *Atg5* and *Atg7* Nestin-Cre models. The variability observed between models will likely be accounted for by the stages at which autophagy is disrupted as well as non-autophagy functions for each target.

To further delineate the function of autophagy in different neuronal types, targeted knockouts of *Atg5* and *Atg7* in Purkinje neurons of the cerebellum (Komatsu et al., 2006; Nishiyama et al., 2007), *Atg7* in Agouti Related Peptide (AgRP) neurons of the hypothalamus (Kaushik et al., 2011), as well as *Atg5* and *Atg7 in* Rhodopsin neurons of the retina (Chen et al., 2013; Zhou et al., 2015) have been developed. Deletion of *Atg5* and *Atg7* results in cell-autonomous Purkinje neuron degeneration. The earliest signs of homeostatic disruption in these mice are Purkinje axonal swellings, which are observed prior to progressive dystrophy and degeneration of the axon (Komatsu et al., 2007b; Nishiyama et al., 2007). These findings support a key role of autophagy in axon homeostasis and highlight an early sign of neuronal dysfunction. Studies from cell culture systems have led to the proposal that different neuronal types may have varying capacities to degrade autophagy substrates, such as mutant polyglutamine proteins, and that this correlates with the sensitivity of that cell type to toxicity of aggregate-prone proteins. (Tsvetkov et al., 2013).

In the peripheral nervous system (PNS), a specific role for autophagy in Schwann cell (SC) function has been identified during myelination and re-myelination. In the early postnatal period when myelination is occurring, autophagy is involved in the maturation of SCs, particularly in the reduction of abaxonal cytoplasm volume. In conditional knockouts where ATG7 is absent in SCs, the abaxonal cytoplasm remains abundant and consequently small fiber hypermyelination is observed (Jang et al., 2015). Conversely, autophagy upregulation via rapamycin treatment during the early post-natal period, leads to a greater reduction in abaxonal cytoplasm within the SCs. After nerve injury, myelin debris is cleared by SCs

through a newly described form of selective autophagy named, myelinophagy (Gomez-Sanchez et al., 2015) and this debris clearance is delayed in *Atg7*-SC conditional knockouts (Jang et al., 2016).

In addition to protecting against neurodegeneration, autophagy also regulates neurogenesis. An important role for autophagy in sustaining the post-natal pool of neural stem cells (NSCs) has recently emerged. In the adult brain, NSCs within the sub-ventricular zone (SVZ) of the lateral ventricle wall and subgranular zone (SGZ) of the dentate gyrus can produce new functional neurons in response to physiological and pathological stimuli (Gage, 2000). Ablation of FIP200 results in a reduced number of NSCs in the SVZ and the dentate gyrus, affecting the self-renewal capacity of NSCs (Wang et al., 2013a). Key autophagy proteins, including AMBRA1 and beclin 1, are highly expressed in the SVZ of adult mouse brain and heterozygosity for *beclin 1* results in decreased cell proliferation *in vitro* (Yazdankhah et al., 2014). Depletion of ATG5 in adult NSC in the dentate gyrus also leads to reduced survival and neuronal maturation (Xi et al., 2016). In all these studies, the depletion of the NSC pool could be attributed to apoptosis (Wang et al., 2013a; Xi et al., 2016; Yazdankhah et al., 2014). However, although apoptosis is likely responsible for reduced survival of autophagy defective NSCs, it is unclear whether NSC differentiation and neuronal maturation is apoptosis-dependent (Xi et al., 2016; Yazdankhah et al., 2014). It will be interesting to examine whether potential beneficial effects of increasing basal autophagy act via changes in NSCs and this is likely to be an exciting topic for future research. In addition to effects on the stem cell pool, autophagy is required for normal neural progenitor cell proliferation and differentiation, as revealed by studies in ubiquitous ATG16L1 hypomorph mice and knockdown of ATG5 *in vivo* in embryonic brains (Lv et al., 2014; Wu et al., 2016).

While impairment of autophagy is deleterious, autophagy upregulation appears to be protective in many normal contexts. Studies in *C. Elegans* have shown a clear association between increased longevity and constitutive autophagy, which may be mediated through multiple different but over-lapping mechanisms, including nutrient restriction (Hansen et al., 2008), altered mitosis (Ghavidel et al., 2015) and mitochondrial turnover (Palikaras et al., 2015). Similarly, pan-neuronal over-expression of Atg8a (Simonsen et al., 2008) or AMPK (Ulgherait et al., 2014) in *Drosophila* resulted in extended lifespan. Overexpression of ATG5 in mice induces autophagy and extends lifespan, and is associated with anti-ageing phenotypes including leanness, increased insulin sensitivity and improved motor function (Pyo et al., 2013). In Huntington's Disease (HD), expansion of the polyglutamine tract in the huntingtin (HTT) protein causes disease with a polyglutamine length-dependent severity. In

mice where the polyglutamine expansion was removed from the endogenous *Htt*-coding gene, (delta-Q mice), an increase in autophagosome biosynthesis was observed and this was also associated with significantly longer lifespan. (Zheng et al., 2010). Together, these studies indicate a beneficial effect of enhancing basal autophagy during aging.

Neurodegenerative Diseases where Autophagy is Impaired

As outlined above, there is increasing evidence for the physiological importance of autophagy in neuronal health, raising the possibility that autophagy dysfunction may play a role in neurodegenerative diseases. Circumstantially, this is further supported by the major pathological phenotype of most late-onset neurodegenerative diseases, the presence of intraneuronal aggregates of misfolded proteins, which are substrates for autophagic degradation (Menzies et al., 2015a; Ravikumar et al., 2002). In some forms of disease, these aggregate-prone proteins are the result of specific mutations (such as in Huntington's disesase). However, in the vast majority of diseases, the underlying reason for the presence of aggregates is unknown.

For the most part, neurodegenerative diseases do not follow simple, monogenic inheritance patterns. However, in all major neurodegenerative diseases, a subset of cases are associated with inherited genetic mutations. These familial forms of disease allow an insight into the potential mechanisms of pathogenesis. Identification of disease-associated genes, and investigations into their functions, reveal that many impact autophagy. The absolute contribution of autophagy dysfunction to disease progression has yet to be established. Given that many neurodegenerative diseases are late-onset, it is possible that small alterations in the turnover of proteins will have cumulative effects that manifest later in life.

The autophagy pathway is complex, with multiple steps and modes of regulation. This makes identifying potentially minor perturbations in the pathway difficult. Therefore, in some cases, the evidence for autophagy involvement in neurodegenerative disease pathogenesis appears controversial. This evidence is discussed in a disease-specific manner below (figure 3).

Alzheimer's Disease

The pathological hallmarks of Alzheimer's Disease (AD) are intracellular tau tangles and extracellular Amyloid Beta (Aβ) plaques. Aβ is formed from Amyloid precursor protein (APP)

by two cleavage events. There is a complex interplay between Aβ and autophagy. Aβ may be degraded by autophagy and upregulation of autophagy has been shown to reduce Aβ levels in a number of systems (Boland et al., 2008; Spilman et al., 2010; Tian et al., 2011; Vingtdeux et al., 2011). However, Aβ may also be generated in autophagosomes, which appear to contain both APP and Presenilin-1 (PS-1), an enzyme involved in the cleavage of APP to Aβ (Boland et al., 2008; Yu et al., 2005). Furthermore, autophagy may play a role in the secretion of Aβ into the extracellular space, where it forms plaques, as deletion of ATG7 in APP transgenic mice results in less Aβ extracellular secretion and plaque formation, contrary to what one may expect if autophagy simply degraded Aβ (Nilsson et al., 2013).

Genetic studies have implicated Phosphatidylinositol Binding Clathrin Assembly Protein (*PICALM*) in Alzheimer's disease (Harold et al., 2009; Jun et al., 2010) and changes in the level of this protein have been reported in the brains of patients with Alzheimer's (Ando et al., 2013; Ando et al., 2016). PICALM is a clathrin adapter protein required for the endocytosis of SNAREs (Soluble NSF Attachment Protein Receptors) and loss of this function has been demonstrated to inhibit autophagy at multiple steps, including early autophagosome formation and maturation of autophagosomes (Moreau et al., 2014). Of course, altered trafficking of these SNAREs is also likely to impact upon other vesicle trafficking pathways and therefore, as with all of the disease mutations discussed in this review, it is yet to be established if, or how much, PICALM-mediated autophagy perturbation contributes to disease. However, a second mechanism through which PICALM function may impact on autophagy has also been proposed. Through its action in a complex with assembly polypeptide 2 (AP2), PICALM may act as an autophagy receptor, which is able to interact with LC3 and target APP into autophagosomes (Tian et al., 2013).

Mutations in *PS-1* cause familial AD, and there is a great deal of evidence demonstrating that these mutations change the way the APP protein is processed (for example (Citron et al., 1997). However, other functions of PS-1 may also contribute to disease pathogenesis. PS-1 has been shown to function as an ER chaperone for the V_0a_1 subunit of the lysosomal v-ATPase. Familial AD associated mutations in PS-1 result in decreased maturation of the lysosomal v-ATPase and thus increased lysosomal pH (Coffey et al., 2014; Lee et al., 2010; Wolfe et al., 2013), which would be predicted to reduce autophagosome clearance.
Autophagy may also be affected by reduced levels of beclin 1 mRNA and protein, which have been reported in AD brains (Pickford et al., 2008; Small et al., 2005). Similarly, beclin 1 protein levels are thought to be decreased due to caspase 3 cleavage, which is activated in the brains of AD patients (Rohn et al., 2011).

Tauopathies

Tau accumulation into intracellular tangles is one of the hallmark pathologies of AD, and is also seen in a group of neuronal disorders termed tauopathies, which include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and frontotemporal dementias (FTDs) (Lee et al., 2001). Hyperphosphorylated tau co-localizes with LC3-positive vesicles and the autophagy cargo-receptor p62/SQSTM1 in CBD and PSP patients (Piras et al., 2016). Moreover, aberrant tau appears to disrupt axonal vesicle transport by impairing the dynein-dynactin complex, increasing the number of autophagosomes and contributing to tau-induced toxicity in FTDs and AD (Butzlaff et al., 2015; Majid et al., 2014). Tau has also been shown to bind lysosomal membranes and impair lysosomal permeability in vitro and in a mouse model of AD (Collin et al., 2014; Wang et al., 2009). Defective lysosomal membrane integrity was also found in AD patients (Perez et al., 2015) and more recently, increased levels of the lysosomal components LAMP1 (Lysosomal-associated membrane protein 1) and cathepsin D were reported in CBD and PSP patients (Piras et al., 2016).

Parkinson's Disease

Compelling evidence supporting a role for dysfunctional autophagy as a causative factor in neurodegenerative disease comes from the studies of mitophagy in Parkinson's Disease (PD). Autosomal recessive forms of early-onset PD are associated with mutations in genes encoding PINK1 (phosphatase and tensin homolog-induced putative kinase 1) (Valente et al., 2004) and the E3 ubiquitin ligase, Parkin (Kitada et al., 1998). Elegant studies have demonstrated that PINK1 and Parkin act in the same pathway to promote mitophagy. PINK1 is stabilised on the outer membrane of damaged mitochondria, leading to the recruitment and activation of the E3 ubiquitin ligase, Parkin, on these mitochondria and ultimately their sequestration into autophagosomes (Matsuda et al., 2010; Narendra et al., 2008). This disease-associated mitophagy signalling pathway has been the subject of recent comprehensive reviews (Pickrell and Youle, 2015; Nguyen et al., 2016).

Several models have been generated to elucidate the function of these mitophagy effectors in the nervous system. Although no gross behavioural changes were found in mice where *Parkin* was deleted (Goldberg et al., 2003; Itier et al., 2003; Perez and Palmiter, 2005; Von Coelln et al., 2004), the activity of striatal neuron mitochondria was impaired (Palacino et al., 2004). A deficit in evoked dopamine release response and striatal synaptic plasticity in the

striatum was also observed (Kitada et al., 2009). Similarly, deletion of the *Pink1* resulted in impaired respiration in striatal mitochondria and increased sensitivity to oxidative stress (Gautier et al., 2008). Furthermore, dopaminergic neurons derived from *Pink1* or *DJ-1* knockout mice also showed defective morphology and reduced activity (Shim et al., 2011). Indeed, loss of endogenous Parkin synergises with a loss of DNA polymerase γ that results in increased mitochondrial mutations, to result in dopaminergic neuron damage (Pickrell et al., 2015). The use of a recently generated reporter mouse to assess *in vivo* mitophagy will shed light on how mitophagy flux is modulated in response to different genetic and pharmacological perturbations (Sun et al., 2015).

Parkinson's Disease (PD) is characterized by loss of dopaminergic neurons in the substantia nigra and typically by presence of α-synuclein (α-syn) inclusions. These inclusions have been shown to impact upon autophagy function (Tanik et al., 2013). In cells with α-syn inclusions, whilst lysosomal function appears normal, autophagosome maturation and fusion with the lysosomes is decreased, resulting in a decrease in protein degradation. It is interesting to note that this alteration in vesicle trafficking does not seem to result from a non-specific physical blockade of the axons by the inclusions, but rather a specific inhibition of endocytic and autophagic vesicles (Volpicelli-Daley et al*.,* 2014). Independently of the formation of inclusions, increased levels of α-syn (as found in disease) has been shown to impair autophagy, as α-syn overexpression in cell and mouse models led to mislocalization of mATG9 (Winslow et al., 2010). Similarly, abnormal trafficking of mATG9 has been shown to be caused by the VPS35 (Vacuolar protein sorting-associated protein 35) D620N mutation, which causes an autosomal dominant form of PD. VPS35 is a component of the retromer complex which recruits the actin nucleation-promoting WASH (WASP and Scar homologue) complex to endosomes. D620N VPS35 prevents this recruitment and thus causes mATG9 mislocalisation and autophagy impairment (Zavodszky et al., 2014).

The most common genetic risk factor for PD is heterozygosity for mutations in the lysosomal enzyme glucocerebrosidase (GBA). These mutations have been reported in up to 31·3% of Ashkenazi Jewish patients with Parkinson's disease, and up to 9·4% in patients of other ethnic origins (Sidransky and Lopez, 2012). Homozygous GBA mutations cause the lysosomal storage disorder Gaucher disease (reviewed in Michel et al., 2016), where loss of GBA leads to the accumulation of its substrate, glucosylceramide within lysosomes and thus to autophagy impairment due to lysosomal dysfunction. In PD patients without GBA mutations, the levels and activity of the enzyme are decreased in brain areas with increased α-syn levels in early disease stages (Mazzulli et al., 2011; Murphy et al., 2014).

Loss of function mutations in the P-type ATPase, ATP13A2 (also known as PARK9), cause familial Kufor-Rakeb syndrome, characterized by early-onset Parkinsonism (Ramirez et al., 2006). Lysosomal ATPases are required for the maintainance of lysosomal pH and therefore the activity of lysosomal proteases. Mutations in *ATP13A2* impair these processes and lead to an increase in the number of autophagic vesicles, which are unable to fuse with lysosomes (Dehay et al., 2012). Impaired lysosomal degradative capacity in cells with ATP13A2 mutations leads to an accumulation of α-synuclein, which may contribute to the toxicity of ATP13A2 mutations. (Usenovic et al., 2012). Recent studies show that ATP13A2 depletion leads to a decrease in the levels of another PD-associated gene, synaptotagmin 11 (SYT11), and that it is this SYT11 decrease which causes lysosomal dysfunction and impaired autophagosome degradation resulting from loss of ATP13A2 activity. Overexpression of SYT11 in ATP13A2-knockdown cells is able to rescue the autophagy defects seen in these cells, demonstrating that they act in the same pathway (Bento et al., 2016a).

Polyglutamine disorders

Nine neurological disorders are caused by mutant proteins with expanded glutamine repeats (polyQ), including Huntington's disease (HD), various spinocerebellar ataxias (SCAs) and spinal and bulbar muscular atrophy (SBMA). Autophagy perturbation is observed in several of these diseases. At the transcriptional level, mutant polyQ androgen receptor (that causes SBMA) interacts with transcription factor EB (TFEB), a potent autophagy gene inducer, and inhibits TFEB transactivation (Cortes et al., 2014). A transgenic mouse model of SCA3 showed low levels of sirtuin 1 (Cunha-Santos et al., 2016), an enzyme that normally deacetylates several autophagy proteins to promote autophagy (Huang et al., 2015; Lee et al., 2008). Additionally, brains from mutant SCA3 transgenic mice have low levels of Parkin (Durcan et al., 2011), and beclin 1 (Nascimento-Ferreira et al., 2011). Beclin 1 appears to be sequestered into aggregates in the brains of mouse models of HD and SCA7 (Alves et al., 2014; Shibata et al., 2006).

The most investigated polyQ disease protein is huntingtin, mutated in HD. Mutant huntingtin impairs efficient cargo recognition by autophagosomes (Martinez-Vicente et al., 2010), while wild-type huntingtin serves as a scaffold for the recruitment of several autophagy proteins during selective autophagy of targets, such as mitochondria and protein aggregates (Ochaba

et al., 2014; Rui et al., 2015). Furthermore, a role for huntingtin in axonal transport of autophagosomes has been suggested by live cell imaging studies in striatal neurons. Following either loss of huntingtin, or expression of the mutant protein, a decrease autophagosome transport and subsequent inhibition of substrate degradation was observed (Wong and Holzbaur, 2014a). Mutant huntingtin also interacts with and inactivates Rhes, a protein selectively expressed in the striatum, the brain region selectively affected in HD. Rhes is required for autophagy as it interacts with beclin 1 and reduces the inhibitory interaction of Bcl-2 with beclin 1 (Mealer et al., 2014). Another important autophagy negative regulator, mTOR, is sequestered to aggregates in HD and SCA7 brains (Alves et al., 2014; Ravikumar et al., 2004).

In addition to potential mechanistic roles in autophagy, it has also been proposed that mutant huntingtin may accumulate due to the loss of an acetylation signal which would normal target it for degradation by this pathway (Jeong et al., 2009). Overall, mutant huntingtin is involved in different pathways that modulate autophagy - some are toxic and others which may be protective. The overall outcome in terms of autophagy activity may depend on the ratio of soluble to aggregated mutant protein.

Amyotrophic Lateral Sclerosis

ALS is associated with the accumulation of misfolded proteins such as SOD1 (Superoxide dismutase 1), TDP-43 (TAR DNA-binding protein 43), FUS (Fused in Sarcoma/Translocated in Sarcoma) and/or C9ORF72 (reviewed in Blokhuis et al., 2013). It is most commonly a sporadic disease but approximately 5-10% of cases are familial. A range of genes have been associated with the disease, but recently it has become apparent that a number of these genes encode for proteins that act as autophagy receptors, SQSTM1/p62 (Fecto et al., 2011), OPTN (Maruyama et al., 2010) and Ubiquilin 2 (Williams et al., 2012), which enhance the incorporation of autophagy substrates into autophagosomes via interactions with LC3, as discussed above (Khaminets et al., 2016). Mutations in SQSTM1/p62 have been associated with disrupted autophagic degradation of mutant SOD1 and TDP-43 (Gal et al., 2009; Teyssou et al., 2013). ALS-causing mutations in the LC3 binding region of SQSTM1/p62 have been shown to impair its recruitment into autophagosomes (Goode et al., 2016). However mutations have been identified throughout the length of the protein and it is not clear how these mutations impact upon SQSTM1/p62 function. Similarly, disease-causing mutations in OPTN decrease autophagy and protein clearance (Shen et al., 2015) and also inhibit the ability of OPTN to recruit LC3 to damaged mitochondria and induce mitophagy

(Wong and Holzbaur, 2014b). OPTN also functions to bind LC3 and Myosin VI, which is required for the trafficking of autophagosomes (Tumbarello et al., 2012), the majority of ALS-associated mutations in OPTN are located in the myosin VI-binding domain and show loss of this binding (Shen et al., 2015; Sundaramoorthy et al., 2015). Recently, mutations in TANK-binding kinase 1 (TBK1) have been associated with ALS (Cirulli et al., 2015; Freischmidt et al., 2015), TBK1 has been shown to phosphorylate OPTN to promote efficient mitophagy and p62 to allow autophagosome maturation (Moore and Holzbaur, 2015; Pilli et al, 2012). Disease-associated mutations in this kinase have been shown to reduce binding of TBK1 to OPTN and thus decrease the clearance of dysfunctional mitochondria (Richter et al., 2016).

Alongside autophagy receptor proteins, other ALS-associated genes have been identified as having a role in autophagy. Disruption of the ESCRT machinery through mutations in charged multivesicular body protein 2B (CHMP2B) have been associated with both ALS and Frontotemporal Dementia, a neurodegenerative disease thought to be on a spectrum with ALS. Disease-associated mutations in CHMP2B impair autolysosome formation and lead to the accumulation of protein aggregates (Filimonenko et al., 2010; Lee et al., 2007).

The most common cause of ALS is a hexanucleotide repeat expansion in the C9ORF72 gene (DeJesus-Hernandez et al., 2011; Renton et al., 2011). These mutations may cause disease through a number of different mechanisms, including toxic gain-of-function from ATG-independent translation of the RNA repeats and loss of normal protein function (Todd and Petrucelli, 2016). A role has been suggested for C9ORF72 in endocytic vesicle trafficking and autophagy (Farg et al., 2014). Recently, C9ORF72 was found to form a complex with SMCR8 (Smith-Magenis Syndrome Chromosome Region, Candidate 8) and WDR41 (WD Repeat Domain 41) (Sellier et al., 2016; Sullivan et al., 2016). This complex acts as a GDP/GTP exchange factor (GEF) for the activation of Rab8 and Rab39, which are involved in the formation or maturation of autophagosomes (Pilli et al, 2012; Seto et al., 2013) and interacts with the autophagy receptors SQSTM1/p62 and OPTN (Sellier et al., 2016). Furthermore, C9ORF72 can interact with ULK1, a key kinase in the control of autophagosome formation and this interaction mediates the translocation of the ULK1 autophagy initiation complex to the phagophore via RAB1a (Webster et al., 2016). Understanding the role of these genes in autophagy may be beginning to provide a link in pathogenic mechanism between ALS genes, as, for example, Rab8 has been identified as a modifier of toxicity in a Drosophila mutant CHMP2B model (West et al., 2015). Finally, another Rab GEF, Alsin (ALS2), has been associated with ALS (Yang et al., 2001). Alsin is

an activator of Rab5 (Topp et al., 2004), which has previously shown to regulate autophagy (Otomo et al., 2011; Ravikumar et al., 2008).

Hereditary Spastic Paraplegia

Hereditary spastic paraplegia (HSP) is a heterogeneous group of neurodegenerative diseases characterized by length-dependent degeneration of upper motor neuron axons resulting in progressive lower limb spasticity. To date, more than 70 distinct loci (SPG1-72) and 50 spastic paraplegia genes have been identified, the type of HSP is designated by the loci it is associated with (ie SPG1-56)(Fink, 2013). *SPG11*, encoding spatacsin, is the most prevalent gene mutated in autosomal recessive HSP. Spatacsin knock-out mice have a reduced number of lysosomes in Purkinje cells and impaired autophagic lysosome reformation in neurons (Varga et al., 2015). SPG11 and SPG15 (encoding spastizin) are both similar in their symptoms and in their cellular mechanisms; loss or mutation of either gene disrupts autophagosome maturation and lysosomal biogenesis (Chang et al., 2014; Renvoise et al., 2014). Spastizin also interacts with the beclin 1-UVRAG-Rubicon complex required for autophagosome maturation (Vantaggiato et al., 2013).

A rare form of HSP is caused by mutations in TECPR2 (tectonin β-propeller containing protein 2) encoded by SPG49. The loss of TECPR2 results a reduction in levels of LC3, along with a reduction in lipidation of LC3 (Oz-Levi et al., 2012). TECPR2 contains an LC3-interacting region (LIR) and its interaction with LC3 is required for maintenance of functional ER exit sites (Stadel et al., 2015). In patient fibroblasts with TECPR2 mutations, ER exit is inhibited and this loss is associated with decreased autophagosome formation.

Lafora disease

Lafora disease is a progressive neurodegenerative disease which manifests with myoclonus epilepsy caused by loss-of-function mutations in either malin or laforin, which form a complex. A characteristic feature of the disease is the formation of inclusions of insoluble forms of glycogen called polyglucosan bodies (or lafora bodies). As malin and laforin have been implicated in glycogen metabolism, it was originally assumed that perturbations in this function cause Lafora disease, but there is also clear evidence to support a key role for dysfunctional autophagy in this disease. Knockout mice for both genes show decreased LC3-II levels, and this is thought to result from increased mTOR activity in the case of mutations in laforin (Aguado et al., 2010; Garyali et al., 2014), although the mTOR

involvement is more controversial in the case of malin mutations (Criado et al., 2012; Garyali et al., 2014).

Charcot-Marie-Tooth (CMT) disease

CMT diseases are hereditary motor and sensory peripheral neuropathies caused by inherited mutations in genes encoding either myelin-related (CMT type 1, CMT1) or axonal (CMT type 2, CMT2) proteins (Bird, 1993a). CMT type 1 X-linked disease, one of the most common neurological disorders, is caused by loss-of-function mutations in the gene *GJB1* encoding the gap junction protein, connexin 32 (Bird, 1993b; Xie et al., 2016). Recent studies reported that connexin 32 depletion reduces autophagosome biogenesis, not via its gap junction function, but rather through directly interacting with autophagy core proteins (VPS34, BECN1, ATG16L1) to sequester them at the plasma membrane (Bejarano et al., 2014). Upon starvation-induced autophagy, ATG14 localizes with a complex containing connexins and several autophagy proteins, facilitating the recruitment of ATG9 and formation of autophagosomes required for the degradation of connexins (Bejarano et al., 2014). However, these data have not yet been validated in neurons or in the context of CMT1.

The genes associated with the axonal CMT type 2 disease include those encoding the dynein-dynactin motor protein complex, also known to cause distal spinal and bulbar muscular atrophy (Puls et al., 2005; Punetha et al., 2015). Many of these mutations impact trafficking pathways relevant to autophagy. *DYNC1H1* (dynein heavy chain 1) mutations, found in some familial cases of CMT2, directly affect neuronal retrograde axonal transport and phenocopy disease pathogenesis in rodent models (Weedon et al., 2011). Additionally, dynein mutations impair autophagosome-lysosome fusion by reducing the retrograde trafficking of autophagosomes to the microtubule organising centre where lysosomes are clustered. This causes reduced autophagic clearance and accumulation of the aggregate-prone proteins (Jahreiss et al., 2008; Ravikumar et al., 2005). Other supportive evidence shows that mutations in the p150 subunit of dynactin cause motor neuron degeneration and result in protein aggregation (Levy et al., 2006). Additional genes affected in some cases of CMT2 encode endocytic-regulatory proteins, such as dynamin. Both knock-in mice bearing the dynamin 2 mutations (Durieux et al., 2012) and *Drosophila* models (*Shi* orthologue loss-of-function) (Fang et al., 2016) showed accumulation of immature autophagosome structures due to defects in autolysosome acidification, rather than affecting the fusion step *per se*. Mutations in genes encoding proteins involved in endosomal maturation, such as RAB7,

lead to impaired autophagic flux (Ganley et al., 2011; Spinosa et al., 2008). A recent characterized CMT2 mutation in *VCP* (Valosin-containing protein) leads to a similar phenotype: accumulation of immature autophagosome and impaired autophagic flux (Gonzalez et al., 2014).

Lysosomal Diseases

Lysosomal diseases are rare, inherited disorders with variable phenotypes. They represent the most common cause of neurodegeneration in childhood but can also result in neurological impairment in adults (Poupetova et al., 2010; Wraith, 2002). Most lysosomal storage disorders are caused by loss-of-function of specific lysosomal hydrolases, leading to the accumulation of the substrates of these enzymes and accumulation of general autophagic substrates due to impaired autophagosome-lysosome fusion (Ballabio and Gieselmann, 2009; Platt et al., 2012; Settembre et al., 2008).

There is increasing evidence that changes in membrane lipid composition as a result of lysosomal dysfunction contribute to lysosome fusion defects. In mouse models of Mucopolysaccharidosis Type III (Sanfilippo Syndrome), defects in the breakdown of heparin sulfate cause an altered membrane lipid composition, with SNARE protein redistribution resulting in impaired autophagosome-lysosome fusion and a block in autophagy (Fraldi et al., 2010; Settembre et al., 2008). The accumulation of the glycosphingolipid psychosine in Krabbe disease, caused by a defect of β-galactocerebrosidase, alters membrane lipid composition (Hawkins-Salsbury et al., 2013). In Niemann-Pick type A disease, where mutations in the gene encoding acid sphingomyelinase cause accumulation of sphingomyelin, defects of mATG9 trafficking and autophagosome closure have also been observed (Corcelle-Termeau et al., 2016). Sphingomyelin storage also leads to lysosomal membrane permeabilization, thereby liberating cathepsins into the cytosol (Serrano-Puebla and Boya, 2015).

Apart from mutations in genes encoding lysosomal hydrolases, defects in posttranslational modifications, impaired trafficking of lysosomal enzymes or defective acidification also result in lysosomal dysfunction (Colacurcio and Nixon, 2016; Hirst et al., 2015; Kyttala et al., 2005; Morimoto et al., 1989; Tiede et al., 2005). One example is Multiple Sulfatase Deficiency in which a failed posttranslational modification of sulfatases by an ER resident enzyme abrogates the function of a whole group of lysosomal hydrolases (Dierks et al., 2009).

Beside this, impaired lysosomal structure, regeneration, fusion and signalling also contribute to lysosomal malfunction (Blanz et al., 2010; Chang et al., 2014; Cortes et al., 2014; Endo et al., 2015; Yu et al., 2010). For example, Niemann-Pick disease Type C, caused by loss of NPC1 function, leads to impaired Ca^{2+} homoeostasis and incorrect cholesterol trafficking with accumulation of unesterified cholesterol and glycosphingolipids in lysosomes and late endosomes, disrupting their fusion (Lloyd-Evans et al., 2008; Lloyd-Evans and Platt, 2010; Pacheco and Lieberman, 2008).

Recently, the group of diseases associated with lysosomal dysfunction has expanded. Mutations in SNX14, a sorting nexin phosphoinositol binding protein localized on the late endosome and lysosomal membrane and involved in cargo sorting upon endocytosis, were found in patients with hereditary cerebellar ataxia. Autophagosome clearance was slowed in patient cells, suggesting lysosome-autophagosome dysfunction (Akizu et al., 2015). A specific role of the autophagosome-lysosome fusion for lysosomal disease pathology is underlined by the discovery of a missense mutation in VPS11 in patients with a rare form of leukoencephalopathy. VPS11 is a member of the HOPS (homotypic fusion and protein sorting) and CORVET (class C core vacuole/endosome tethering) complexes and mutations lead to impaired autophagy. A zebrafish VPS11 mutant (*vps11(plt)*) shows a reduction in CNS myelination and extensive neuronal death in the hindbrain and midbrain (Zhang et al., 2016).

Core autophagy genes implicated in neurodegenerative disease

As outlined above, mutations in what might be termed “autophagy accessory” genes have been identified in a number of diseases, but diseases have also been identified which result from mutations in core autophagy genes. Recently an E122D *ATG5* mutation was identified in two siblings with childhood ataxia characterized by lack of coordination and cerebellar hypoplasia (Kim et al., 2016). The E122D mutation weakens binding of ATG5 to ATG12 resulting in decreased autophagosome formation and reduced autophagy flux.

Another autophagy gene involved in disease is WDR45, a gene coding for the protein WIPI4, one of the four WIPI proteins (Proikas-Cezanne et al., 2004). WIPI proteins are key autophagic lipid sensors that facilitate autophagosome maturation by bridging PI(3)P production and LC3 lipidation in mammalian cells (Lamb et al., 2013). *De novo* mutations in WDR45 cause static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) (Haack et al., 2012; Saitsu et al., 2013), also called BPAN (beta-propeller protein-

associated neurodegeneration). In lymphoblastoid cell lines derived from BPAN patients, mutant WDR45 is less stable and degraded, resulting in decreased protein levels compared to unaffected individuals. These cells showed an impairment in autophagy flux and an accumulation of LC3-positive autophagosome membranes (Saitsu et al., 2013). CNS-specific WDR45 knockout mice exhibit some aspects of the BPAN phenotype: poor motor coordination, impaired learning and memory, and extensive axon swelling with numerous axon spheroids, along with autophagy perturbation in the form of accumulation of p62 and ubiquitin positive aggregates (Zhao et al., 2015).

Autophagy therapeutics for Neurodegenerative diseases

The neuropathology of protein misfolding diseases is intimately linked with the propensity of specific proteins to misfold and self-associate, giving rise to an array of oligomers and aggregates. As many of these proteins cause disease primarily via toxic-gain-of function mechanisms, one way of combatting disease is to reduce the levels of such proteins (Ciechanover and Kwon, 2015). Furthermore, most aggregate-prone, neurodegenerative disease-associated proteins have been shown to be autophagy substrates, including mutant huntingtin, alpha-synuclein, and tau (Berger et al., 2006; Ravikumar et al., 2002; Ravikumar et al., 2004; Webb et al., 2003); (Rubinsztein et al., 2012). Importantly, induction of autophagy reduces the levels of both the soluble and aggregated species in such models, and is associated with beneficial effects. It is likely that the autophagic process is capturing small oligomeric species and not the very large aggregates visible by light microscopy - the reduction of the large aggregates after autophagy induction may reflect a reduced input of the smaller species into the aggregates and the flux of the mutant proteins on and off the aggregates (Berger et al., 2006; Ravikumar et al., 2002; Ravikumar et al., 2004; Webb et al., 2003).

Many small molecules employed to induce autophagy have an impact on cellular effectors with pleiotropic effects, such as mTOR and AMPK (Fleming et al., 2011; Levine et al., 2015). Nevertheless, in many cases, the impact of such autophagy modulators on the levels of the substrates have been shown to be autophagy-dependent (e.g.Williams et al., 2008). Supplementary table 1 lists key autophagy enhancing molecules that have been validated *in vivo*, their mechanism of action, biological targets and CNS penetration profiles.

Autophagy inducers can be classified into two main groups; those acting via mTOR-dependent or mTOR-independent targets. mTOR inhibitors are either ATP competitive

inhibitors (e.g. Torin1 and related compounds) or non-ATP competitive inhibitors (e.g. rapamycin and rapalogs) (Kim and Guan, 2015). Due to their inhibition of mTORC1, mTORC2 and in some cases of PI3K activities, chronic dosing of ATP-competitive inhibitors of mTOR activity in animals present significant toxicity issues (Kim and Guan, 2015) and for this reason they are generally unsuitable for studies in mouse models of neurodegeneration, which typically require chronic dosing. While mTORC1 inhibits autophagy, mTORC2 is required for autophagy and the autophagy inhibition resulting from prolonged exposure to such compounds may explain at least some of their toxicity *in vivo* (Renna et al., 2013). Rapamycin and rapalogues have relatively safer profiles owing to their non-ATP competitive mode of action and apparent selectivity for mTORC1 (Wander et al., 2011), allowing everolimus (a rapalogue; (Lebwohl et al., 2013) to be recently approved by the FDA for the treatment of tuberous sclerosis. Rapamycin and its analogues have shown benefits as autophagy inducers in animal models of AD, PD, FTD, HD and PrP (Cortes et al., 2012; Jiang et al., 2014; Menzies et al., 2010; Ozcelik et al., 2013; Ravikumar et al., 2004; Sarkar et al., 2008; Spilman et al., 2010; Wang et al., 2013b). The therapeutic efficacy of rapamycin in SOD1 ALS mouse models is complex, with some studies reporting detrimental effects (Zhang et al., 2011) and others reporting beneficial effects only after uncoupling of it's immunomodulatory function (Staats et al., 2013).

Many mTOR-independent autophagy activators signal via AMPK. Trehalose, a widely studied autophagy inducer in neurodegeneration models (Sarkar et al., 2007), has recently been characterized as acting via AMPK activation (DeBosch et al., 2016). The molecular targets of this disaccharide have been proposed to be GLUT proteins, a family of glucose transporters whose inhibition by trehalose results in AMPK activation (DeBosch et al., 2016). Trehalose dosing in mice has shown therapeutic effects, concomitant with autophagy induction, in an impressive variety of mouse models of neurodegeneration including AD, PD, FTD, HD, SCA17, PrP, ALS, and OPMD (Aguib et al., 2009; Castillo et al., 2013; Chen et al., 2015; Davies et al., 2006; Du et al., 2013; Li et al., 2015; Rodriguez-Navarro et al., 2010; Schaeffer and Goedert, 2012; Schaeffer et al., 2012; Tanaka et al., 2004; Tanji et al., 2015; Zhang et al., 2014).

Metformin is another AMPK-dependent autophagy inducer which has shown beneficial effects in animal models of neurodegeneration. Metformin has shown efficacy in animal models of AD, HD and Lafora disease (Berthier et al., 2016; Ma et al., 2007; Son et al., 2016) but showed no efficacy in ALS models (Kaneb et al., 2011). Berberine, which showed efficacy in an HD model (Jiang et al., 2015), may also induce autophagy via AMPK activation (Yu et al., 2014). Methylene blue, a reported anti-aggregant and AMPK activator (Shin et al.,

2014), was shown to induce autophagy and ameliorate disease phenotype in FTD models (Congdon et al., 2012; Hochgrafe et al., 2015; Melis et al., 2015). Nilotinib, a c-Abl kinase inhibitor and AMPK activator (Yu et al., 2013), was shown to induce autophagy and ameliorate disease phenotype in PD mice (Hebron et al., 2014; Lonskaya et al., 2015).

Finally, a growing number of autophagy inducers are being characterized which may act on other pathways, including compounds acting on the modulation of cAMP/IP3, such as rilmenidine, clonidine, minoxidil and verapamil, which have been shown to ameliorate phenotypes in animal models of HD (Rose et al., 2010; Williams et al., 2008) (Supplementary table 1).

In addition to the small molecules with *in vivo* validation reviewed above, there are further molecules which have been shown to be active in cell-based models but not yet in vivo. These are presented, with their mechanism of action and any available evidence for potential CNS penetration in supplementary table 2.

Non-small molecule approaches

In addition to small molecule therapeutics, a number of other strategies for autophagy enhancement have been adopted. Shoji-Kawata *et al.* have reported the development of a Tat-beclin 1 peptide, which consists of the HIV-1 Tat protein transduction domain linked to a modified 18 amino acid sequence based on the residues 267-284 of beclin 1 (Shoji-Kawata et al., 2013) This region was identified as being required for the autophagy-inducing effects of beclin 1. The Tat-beclin 1 peptide was found to increase autophagic flux via the canonical pathway using a range of cell models and to decrease the number of small huntingtin aggregates in HeLa cells. It was also shown that Tat-beclin 1 increased GFP-LC3 dots in a range of tissues in a transgenic mouse model (Shoji-Kawata et al., 2013).

A number of mouse studies exploring the potential of gene therapy have been reported. For example, delivery of the TFEB gene ameliorates signs of disease in a PD model based on adeno-associated virus (AAV) vector-mediated over-expression of human wild-type α-synuclein in the rat midbrain (Decressac et al., 2013) and in a transgenic mouse model overexpressing tau, TFEB was able to decrease levels of pathological tau and improve cognitive performance and synaptic function (Polito et al., 2014). Beneficial effects have also been reported with beclin-1 over-expression in an α-synuclein model of PD/Lewy Body Diseases (Spencer et al., 2009), and in a model of Machado-Joseph disease (Nascimento-

Ferreira et al., 2011). Parkin overexpression has beneficial effects in an AD model (Khandelwal et al., 2011).

Another possible candidate target for such approaches is calpain. Knockdown of calpain in an Huntington's disease Drosophila model (RNAi) results in upregulation of autophagy, reduction of huntingtin aggregate number and increases cell survival and is also protective against tau toxicity in HD and tauopathy models, respectively (Menzies et al., 2015b). In mice, neuronal overexpression of calpastatin (CAST), an endogenous inhibitor of calpain, increased autophagy and confers protection when crossed to HD mice, improving aggregate burden, behavioural measures of degeneration and long-term survival (Menzies et al., 2015b). These CAST transgenic mice were compared to wild-type littermates and no deficits were found by SHIRPA behavioural testing or on survival, suggesting that such a strategy may be well tolerated.

Considerations for autophagy as a therapeutic strategy in neurodegeneration

Taken together, the evidence from pharmacological efficacy mouse studies suggests that autophagy activation has significant therapeutic potential across a wide range of neurodegenerative diseases. Whilst the majority of studies of autophagy modulating approaches in neurodegenerative disease models have reported beneficial effects on disease signs, this is not universally true (Hernandez et al., 2012; Komatsu et al., 2007). For example, in the SOD1 G93A mutant model of ALS, treatment with rapamycin decreased lifespan and increased motor neuron degeneration (Zhang et al., 2011). However, rapamycin is protective in such mice lacking mature lymphocytes, suggesting that the immunosuppressive effects of this drug (unrelated to autophagy) may be deleterious in this disease and may counterbalance protective effects of autophagy induction (Staats et al., 2013). Indeed, an alternative mTOR-independent autophagy inducer, trehalose, is protective in this SOD1 ALS model (Zhang et al., 2014).

Similarly the time-point in disease at which autophagy is induced may be critical. For example, many studies have demonstrated the protective effect of autophagy upregulation on α-synuclein toxicity (eg Decressac et al., 2013, Hebron et al., 2014, Spencer et al., 2009). However, at least in tissue culture, α-synuclein aggregate-containing cells appear to have impaired autophagosome maturation, and autophagy upregulation may actually be toxic under these conditions (Tanik et al., 2013). Likewise, the point of intervention in the

autophagy pathway might be an important consideration. For example where autophagosome clearance or degradation is impaired, upstream induction of autophagy may lead to a largely unproductive accumulation of autophagosomes, possibly leading to toxic consequences, this may be avoided by more directly targeting lysosomal function or using approaches that enhance the entire pathway, including increasing lysosomal capacity (for example with TFEB, as discussed above). Thus, one should ideally understand autophagy dynamics in diseases one is aiming to treat in order to best tailor the therapeutic approach to the most suitable diseases. Further developments in autophagy-based therapeutics for neurodegeneration must await the advent of sharper pharmacological tools for autophagy induction, with more selective molecular targets within the autophagic process, and of higher resolution readouts for different steps of the autophagic flux with which autophagy dysfunction in different neurodegenerative diseases can be profiled.

Conclusions

In this review, we have highlighted how autophagy defects at various stages of the pathway may be seen in diverse neurodegenerative conditions, and that autophagy upregulation may be a promising therapeutic strategy for some diseases. However, the roles of autophagy in health and disease may be more complex and not simply cell-autonomous. For example, autophagy impacts inflammatory and immune processes, which are increasingly being implicated in various neurodegenerative diseases (Rubinsztein et al., 2015). Future studies aiming to understand non-cell autonomous effects of autophagy in the nervous system and its relevance to neuronal-glial interactions are likely to be informative.

From a therapeutic perspective, we believe that autophagy is a promising target mechanism. In many cases, it enhances the removal of the primary toxic entity causing disease (e.g. mutant tau or mutant huntingtin), and thus targets such diseases at their roots. Autophagy upregulation also has additional protective effects by reducing susceptibility to pro-death insults (Boya et al., 2005; Ravikumar et al., 2006). One benefit of autophagy upregulation as a therapeutic approach is that one need not require constitutive activation of the pathway, as a pulsatile strategy (like periodically taking out the rubbish) may be sufficient to have efficacy, especially if employed over a long time period. This would have major benefits from a drug toxicity perspective.

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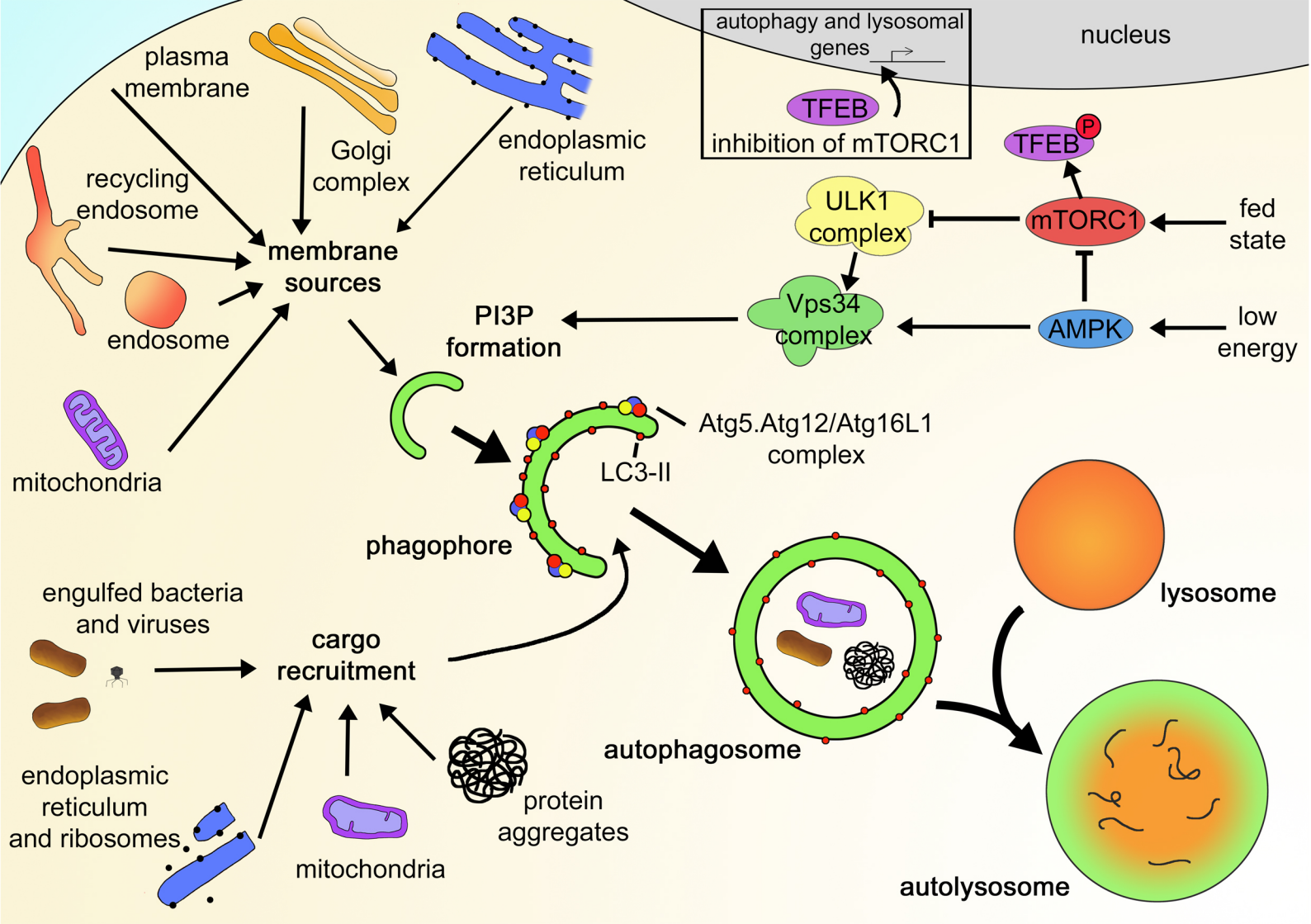
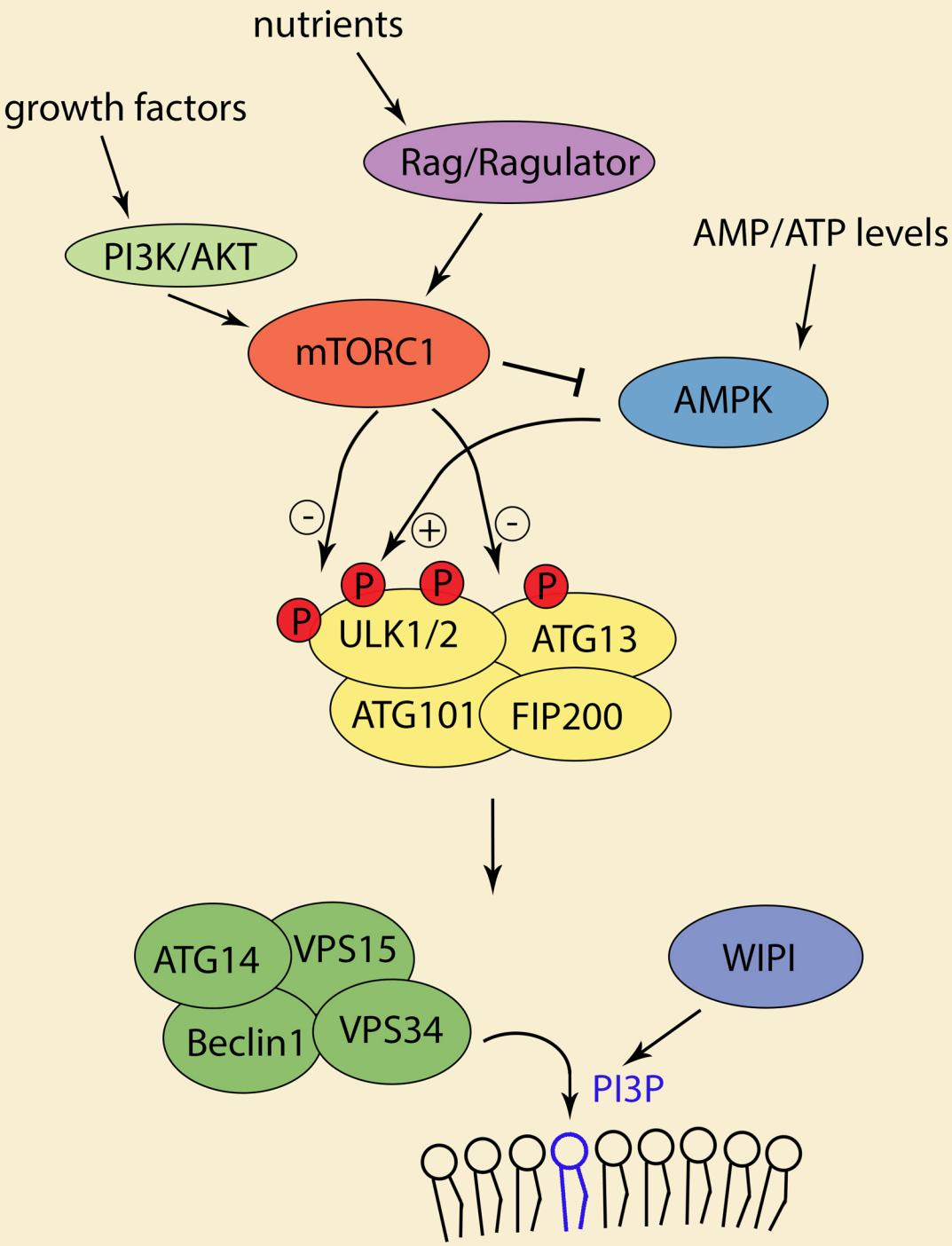
Figure Legends:

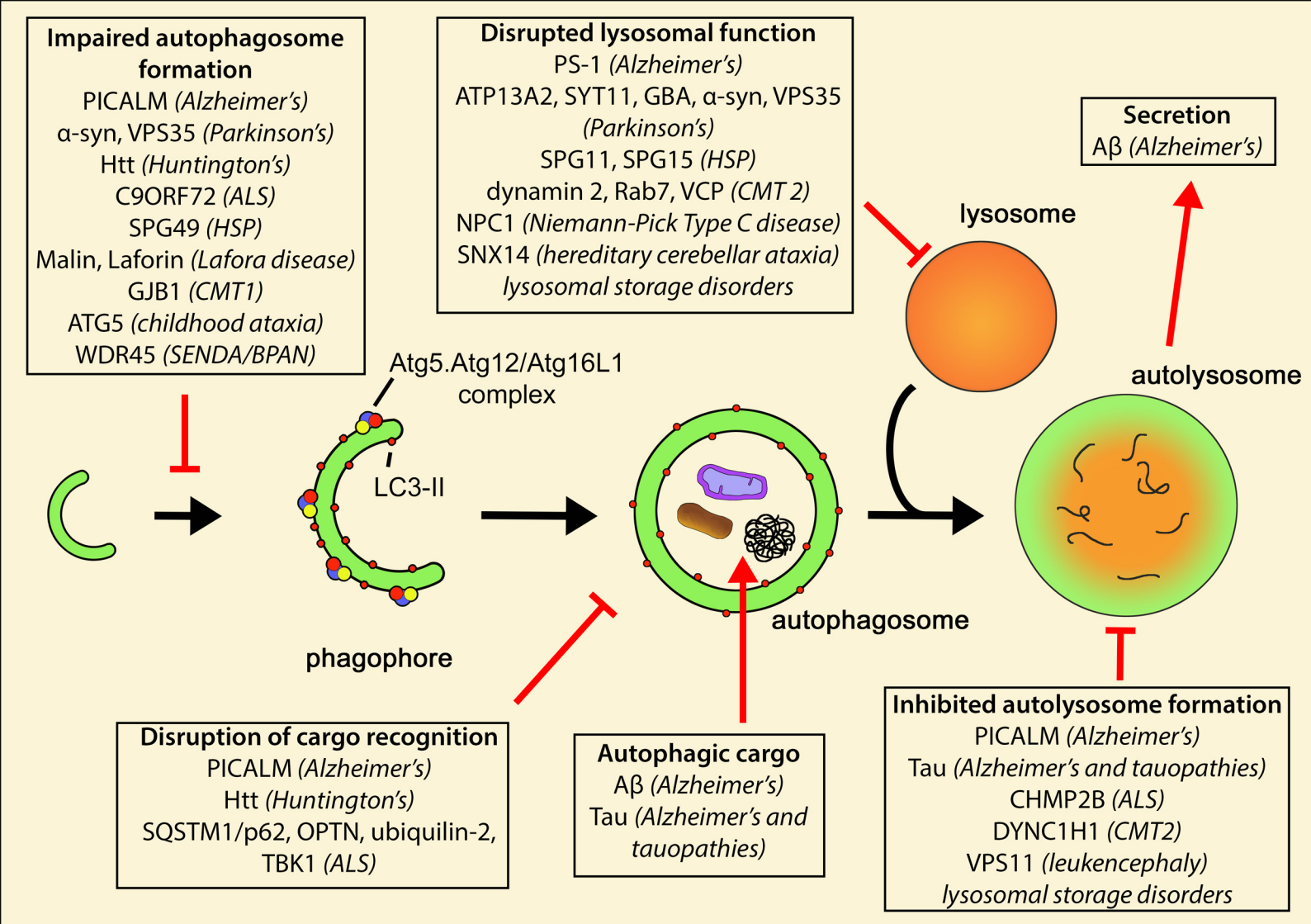
Figure 1. Overview of the mammalian autophagy pathway. Nutrient depletion, growth factors deprivation and low energy are well established autophagy inducers. These culminate in mTORC1 inhibition and AMPK activation, which, in turn, positively regulate the ULK1 complex through a series of phosphorylation events. Induction of the ULK1 complex subsequently activates the VSP34 complex, which leads to PI(3)P synthesis in pre-autophagosomal structures – the membrane of these structures, appear to have multiple sources, such as the endoplasmic reticulum, Golgi apparatus and trans-Golgi network, plasma membrane, endosomal compartment and mitochondria. PI3P defines the LC3-lipidation sites for autophagosome precursors by assisting in the recruitment of the ATG12-ATG5-ATG16L complex. This complex is essential for the conjugation of LC3-I to PE in membranes, which sustains membrane elongation and engulfment of a variety of substrates (e.g. protein aggregates, infectious agents and damaged mitochondria) that end up being degraded in the lysosome after fusion with autophagosomes. Conditions characterized by mTORC1 inactivation are also accompanied by translocation of TFEB to the nucleus and TFEB activation, leading to the transcription of many autophagy and lysosomal genes, which ensure synthesis of key components of the pathway and efficient autophagy-dependent degradation. AMPK, AMP-dependent protein kinase; mTORC1, mammalian target of rapamycin complex 1; PE, phosphatidylethanolamine; PI3P, phosphatidylinositol 3-phosphate; TFEB, transcription factor EB; ULK, mammalian homologs of the *C. elegans* uncoordinated-51 kinase.

Figure 2. Autophagy regulation in response to nutrients. The key signalling pathway controlling autophagy response to nutrient and energy levels converges on the phosphorylation of the ULK1/2 complex at different sites. This phosphorylation regulates the recruitment of the VPS34 complex to the phagophore and hence the production of PI3P and downstream autophagy effectors via the binding of WIPI proteins.

Figure 3. Intersections between autophagy and disease associated genes. An increasing number of genes associated with neurodegenerative diseases have now been implicated in autophagy function. These genes act at a number of different steps throughout the autophagic process, from early steps of autophagosome formation through to autolysosome formation. In the diagram above their proposed site of action is indicated, along with the neurodegenerative disease with which they are associated.


autophagy and lysosomal genes
nucleus
TFEB
inhibition of mTORC1
TFEB
P
plasma membrane
Golgi complex
endoplasmic reticulum
recycling endosome
membrane sources
endosome
ULK1 complex
mTORC1
fed state
Vps34 complex
AMPK
low energy
PI3P formation
mitochondria
Atg5.Atg12/Atg16L1 complex
LC3-II
phagophore
lysosome
engulfed bacteria and viruses
cargo recruitment
autophagosome
endoplasmic reticulum and ribosomes
protein aggregates
mitochondria
autolysosome

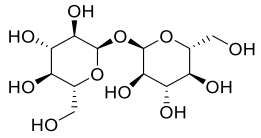
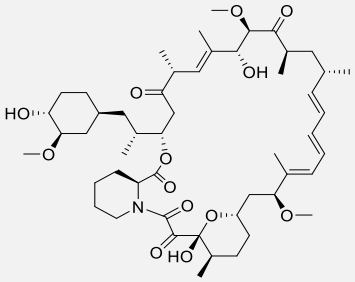
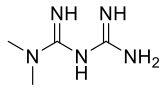
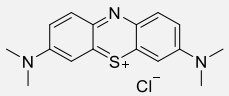
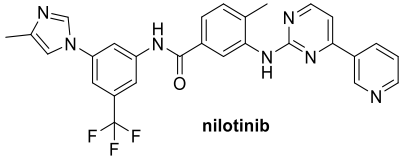

nutrients
growth factors
Rag/Ragulator
PI3K/AKT
AMP/ATP levels
mTORC1
AMPK
P
P
P
P
ULK1/2
ATG13
ATG101
FIP200
ATG14
VPS15
Beclin1
VPS34
WIPI
PI3P

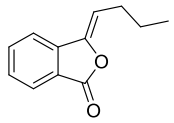
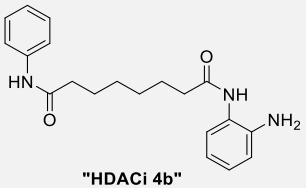
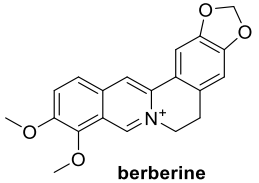
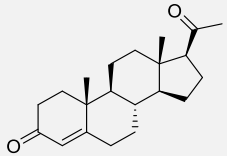
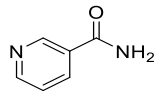
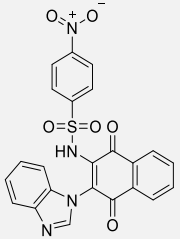
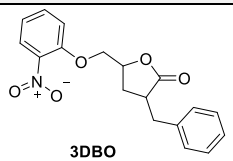

Impaired autophagosome formation
PICALM (Alzheimer's)
α-syn, VPS35 (Parkinson's)
Htt (Huntington's)
C9ORF72 (ALS)
SPG49 (HSP)
Malin, Laforin (Lafora disease)
GJB1 (CMT1)
ATG5 (childhood ataxia)
WDR45 (SENDA/BPAN)
Disrupted lysosomal function
PS-1 (Alzheimer's)
ATP13A2, SYT11, GBA, α-syn, VPS35 (Parkinson's)
SPG11, SPG15 (HSP)
dynamin 2, Rab7, VCP (CMT 2)
NPC1 (Niemann-Pick Type C disease)
SNX14 (hereditary cerebellar ataxia)
lysosomal storage disorders
Secretion
Aβ (Alzheimer's)
lysosome
Atg5.Atg12/Atg16L1 complex
LC3-II
phagophore
autophagosome
autolysosome
Disruption of cargo recognition
PICALM (Alzheimer's)
Htt (Huntington's)
SQSTM1/p62, OPTN, ubiquilin-2, TBK1 (ALS)
Autophagic cargo
Aβ (Alzheimer's)
Tau (Alzheimer's and tauopathies)
Inhibited autolysosome formation
PICALM (Alzheimer's)
Tau (Alzheimer's and tauopathies)
CHMP2B (ALS)
DYNC1H1 (CMT2)
VPS11 (leukencephaly)
lysosomal storage disorders

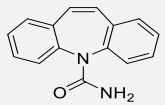
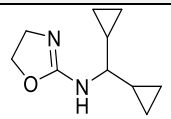
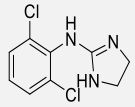
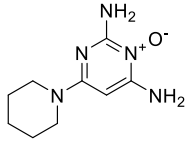
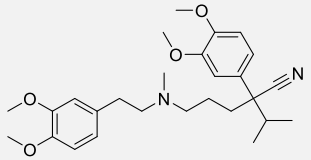
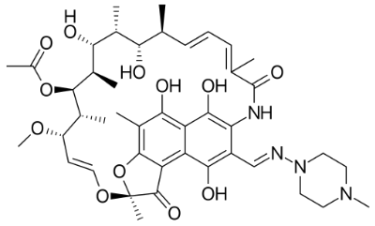
Supplemental Information

Contents

Table S1. Autophagy enhancers with validation in vivo.

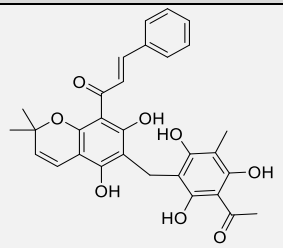
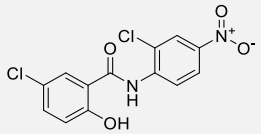
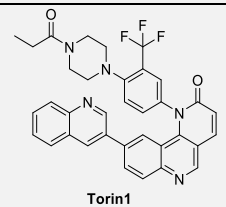
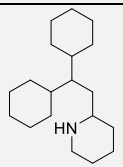
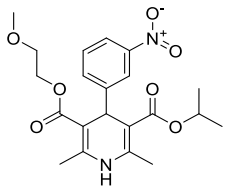
Autophagy Enhancer			Autophagy in vivo			Other properties		
Compound	**Mechanism**	**Target**	**Effect**	**Model**	**Ref**	**CNS penetrant[e]**	**Ref**	**Comments**
 Trehalose	AMPK activation	SLC2A	Induction	AD (APP/PS1)	Du, et al., 2013	Yes[a]	{Tanaka, 2004 #979}	Dietary supplement
				PD (A53T SNCA)	Tanji et al. 2015			
				HD (R6/2)	Tanaka et al., 2004			
				ALS (SOD1)	Castillo et al. 2013; Li et al., 2015; Zhang et al., 2014			
				Prion (PrPsc)	Aguib et al., 2009			
				SCA17	Chen et al., 2015			
				OPMD	Davies et al., 2006			
 Rapamycin	mTOR inhibitor	mTORC1	Induction	AD (PDAPP)	Spilman et al., 2009; Pierce et al., 2013	Yes[a]	{Ozcelik, 2013 #994}	Approved for the prophylaxis of organ rejection[f]
				PD (A53T SNCA)	Bai et al., 2015			
				FTD (TDP-43)	Wang et al., 2013			
				FTD (TAU P301S)	Ozcelik et al., 2013			
				FTD (TAUP 301L)	Siman et al., 2015			
				ALS (SOD1 G93A)	Staats et al., 2013			
				Prion (PrP A116V)	Cortes et al., 2012			
 metformin	AMPK activation	AMPK	Induction	AD (Tg6799)	Son et al., 2016	Yes[a]	Labuzek et al. 2010	Approved for non-insulin-dependent diabetes mellitus[f]
				ALS (SOD1 G93A)	Kaneb et al., 2011			
				HD (R6/2)	Ma et al., 2007			
 methylene blue	AMPK activation	Other (anti-aggregant) MAO inhibitor	Induction	FTD (2N4R Tau-ΔK280)	Hochgrafe et al., 2015	Yes[a]	Peter et al., 2000	Investigational inhibitor of Tau protein aggregation[f]
				ALS (SOD1, TDP-43)	Audet et al., 2012			
 nilotinib	AMPK activation	c-ABL inhibitor	Induction	AD (TgAPP)	Lonskaya et al., 2013a	Poor[a]	Reinwald et al., 2014	Approved leukemia treatment[f]
				PD (A53T SNCA)	Hebron et al., 2013b			
 lithium	cAMP/IP3	IMP inhibitor	Induction	AD (APP/PS1)	Zhang et al., 2011	Yes[a]	Wraae, 1978	Approved for bipolar disorder/epilepsy[f]
				ALS (SOD1 G93A)	Fornai et al., 2007			
				ALS (SOD1 G93A)	Gill et al., 2009			
				ALS (SOD1 G93A)	Pizzasegola et al., 2009			

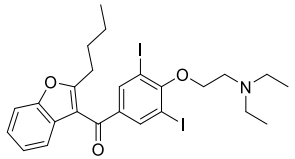
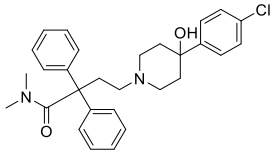
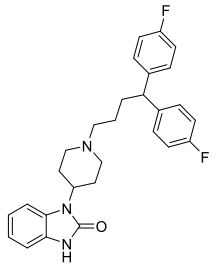
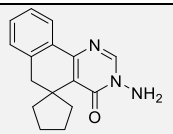
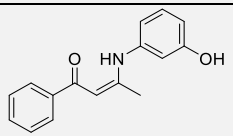
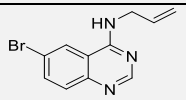
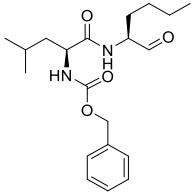
 ***n-butylidinephthalide***	mTOR activation	Other (Unknown)	Suppression	ALS (SOD1 G93A)	Hsueh et al., 2016	ND[c] (TPSA = 26.3 Å^2; MW = 188.2)	None[d]	Investigational probe
 **"HDACi 4b"**	Other	Other (HDAC1/3)	Induction	HD (N171-82Q)	Jia et al., 2012	Poor[a]	Beconi et al., 2012	Investigational probe
 **berberine**	AMPK activation	Other (α-glucosidase inhibitor, stimulation of glycolysis)	Induction	HD (N171-82Q)	Jiang et al., 2015	Yes[a]	Wang et al., 2005	Traditional Chinese medicine
 **progesterone**	Other	Other (NHR agonist)	Induction	ALS (SOD1 G93A)	Kim et al., 2013	Yes[a]	Uhr et al., 2002	Approved progesterone supplementation or replacement[f]
 **nicotinamide**	Other	Other (sirtuin inhibitor)	Induction	AD (3xTG)	Liu et al., 2013	Yes[a]	Hankes et al., 1991	Approved for blacktongue and pellagra[f]
 **AUTEN-67**	Other	Other (MTMR14 inhibitor)	Induction	HD (Drosophila)	Billes et al., 2016, Papp et al., 2016	Yes[a]	Papp et al., 2016	Investigational probe
 **3DBO**	mTOR activation	Other (Unknown)	Suppression	AD (APP/PS1)	Wei et al., 2014	ND[c] (TPSA = 87.3 Å^2; MW = 327.3)	None[d]	Investigational probe

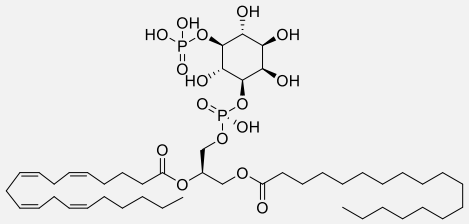
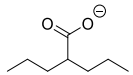
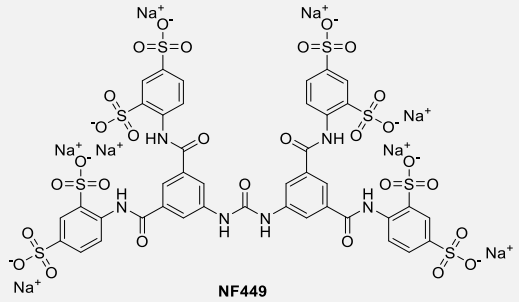
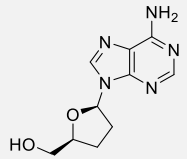
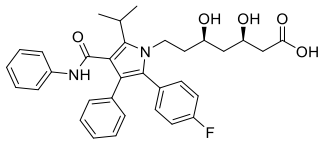
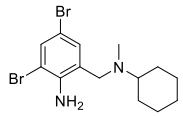
 carbamazepine	mTOR inhibitor	Other (Na Channel inhibitor)	Induction	AD (APP/PS1)	Li et al., 2013	Yes[a]	Fortuna et al., 2013	Approved anitepileptic[f]
 rilmenidine	cAMP/IP3	Other (imidazoline receptors agonist)	Induction	HD (N171-82Q)	Rose et al., 2010	Yes[a]	Montastruc et al., 1989	Approved treatment for hypertension (Remková et al., 2002)
 clonidine	cAMP/IP3	Other (α2-receptors agonist)	Induction	HD (Drosophila and Zebrafish)	Williams et al., 2008	Yes[a]	Castro et al., 1989	Approved centrally-acting anti-hypertensive[f]
 minoxidil	cAMP/IP3	Other (Potassium channel agonist)	Induction	HD (Drosophila and Zebrafish)	Williams et al., 2008	Yes[g]	Nagendra et al., 2003	Approved treatment for androgenic alopecia and hypertension[f]
 verapamil	cAMP/IP3	Other (voltage-dependent calcium channels inhibitor)	Induction	HD (Drosophila and Zebrafish)	Williams et al., 2008	Yes[b]	Narang et al., 1988	Approved class IV anti-arrhythmia agent[f]
 rifampicin	mTOR inhibition	Other (PP2A)	Induction	AD (Tg2576)	Umeda et al., 2016	Poor[a]	Shobo et al., 1998	Approved braod spectrum antibacterial for tuberculosis[f]

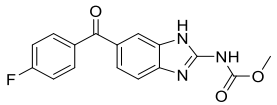
[a]Compound detected in brain or CSF during in animal studies; [b]compound detected in CSF during clinical studies; [c]efficacious in animal models of CNS disorders but no direct measurement of compound in the brain; [d]to the authors' knowledge there have been no reported studies which have directly measured levels of these compounds in CSF or brain tissue; [e]where experimental CNS penetration data are not available, calculated total polar surface area (TPSA) and molecular weight (MW) are provided as predictors of brain penetration (likelihood of being a Pgp substrate increases where TPSA > 60 Å^2 and MW > 400; Rankovic, 2015); [f]information obtained from www.drugbank.ca; [g]mixodinil has been studied in models where the blood-brain barrier is impaired and is known to increase brain penetration through modulation of potassium channels.

Table S2. Selected autophagy enhancers with in vitro activity.

Autophagy enhancers with in vitro activity			**Other properties**		
Compound	**Mechanism**	**Reference**	**CNS penetrant[e]**	**CNS ref**	**comments**
 rottlerin	mTOR inhibition	Balgi et al., 2009	Yes[a]	Zhang et al., 2007	Investigational probe
 niclosamide		Balgi et al., 2009	ND (TPSA = 101.1, MW = 327.1)	None[d]	Approved for the treatment of tapeworm infections[f]
 Torin1		Thoreen et al., 2009	Yes[c]	Vogel et al., 2015	Investigational probe
 perhexiline		Balgi et al., 2009	Yes[b]	Singlas et al., 1978	Approved CPT-1 and CPT-2 inhibitor for angina pectoris[f]
 Nimodipine	Reduction of intracytosolic Ca^{2+} levels	Williams et al., 2008	Yes[a]	Heffez et al., 1985	Ca2+ channel blocker; adjunct to improve neurologic outcome following subarachnoid hemorrhage[f]

 amiodarone		Balgi et al., 2009	Poor[b]	Broekhuysen et al., 1969	Approved class III antiarrhythmic agent[f]
 Loperamide		Williams et al., 2008	Yes[a]	Doran et al., 2005	Approved non-selective calcium channel blocker mu opioid receptor binder for diarrhea[f]
 pimozide		Zhang et al., 2007	Yes[a]	Soudijn et al., 1972	Approved antipsychotic; blocks dopamine and various other receptors[f]
 SMER10	unknown	Sarkar et al., 2007	ND (TPSA = 58.7, MW = 267.3)	None[d]	Investigational probe
 SMER18			ND (TPSA = 49.3, MW = 253.3)	None[d]	Investigational probe
 SMER28			ND (TPSA = 36.7, MW = 264.1)	None[d]	Investigational probe
 calpeptin	Calpain inhibitor	Williams et al., 2008	Yes[c]	Wei et al., 2015	Investigational probe

 PI(5)P	upregulation of autophagosome synthesis	Vicinanza et al., 2015	ND (TPSA = 256.0, MW = 967.1)	None[d]	Endogenous lipid which sustains noncanonical autophagy in PI(3)P-depleted cells (Vicinanza et al., 2015)
 valproate	reduction of Ins(1,4,5)P3 levels	Williams et al., 2008	Yes[a]	Cornford et al., 1985	Approved treatment for epilepsy & bipolar disorder[f]
 NF449	reduction of cAMP levels	Williams et al., 2008	ND (TPSA = 615.1, MW = 1505.1)	None[d]	Investigational probe
 2',5'-deoxyadenosine		Williams et al., 2008	ND (TPSA = 95.8, MW = 235.3)	None[d]	Adenyl cyclase inhibitor; not an approved drug (Williams et al., 2008)
 atorvastatin	AMPK activation	Parikh et al., 2010	Predicted to be poor[g]	Sierra et al., 2011, Lennernas, 2003	Approved lipid lowering treatment. Depletes geranylgeranyl diphosphate and activates AMPK[f]
 bromohexine	TFEB activation	Chauhan et al., 2015	Predicted to be poor	Wiser et al., 2008	Mucolytic agent used in the treatment of respiratory disorders

 flubendazole	mTOR inhibitor	Chauhan et al., 2015	Yes	Tellez-Giron et al., 1984	Antihelmintic

[a]Compound detected in brain or CSF during in animal studies; [b]compound detected in CSF during clinical studies; [c]efficacious in animal models of CNS disorders but no direct measurement of compound in the brain; [d]to the authors' knowledge there have been no reported studies which have directly measured levels of these compounds in CSF or brain tissue; [e]where experimental CNS penetration data are not available, calculated total polar surface area (TPSA) and molecular weight (MW) are provided as predictors of brain penetration (likelihood of being a Pgp substrate increases where TPSA > 60 $Å^2$ and MW > 400; Rankovic, 2015); [f]information obtained from www.drugbank.ca; [g]In vitro studies, atorvastatin is also a known Pgp substrate;

Supplemental References

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